01C10-4
INSIGHTS INTO THE URATE RENAL EXCRETION MECHANISM BASED ON THE DIFFERENCE IN URICOSURIC EFFECTS BETWEEN PROBENECID AND BENZBROMARONE
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The homeostasis of urate, the end product of purine bases, is strictly regulated by hepatic synthesis and urinary excretion. The renal excretion mechanism of urate has been characterized by loading tests of uricosuric agents, such as probenecid (PRB) and benz bromarone (BZB), and the anti-uricosuric agent, pyrazinamide. Both PRB and BZB are inhibitors of URAT1, a transporter responsible for urate reabsorption in the kidney. However, PRB exhibits a uricosuric effect even when pyrazinamide is administered, while BZB has no effect. The purpose of the present study is to investigate the mechanism underlying this discrepancy. We examined the effects of PRB and BZB on the uptake of pyrazinamide (PA), the active form of pyrazinamide, by the kidney in vivo. Neither PRB nor BZB affected the plasma concentration of PA. However, PRB significantly reduced the renal clearance, and kidney-to-plasma concentration ratio of PA to 29 and 42 % of the control values, respectively, while BZB had no effect. Therefore, PRB inhibits the basolateral uptake of PA, which may result in attenuation of the antiuricosuric effect of PA. Meanwhile, we confirmed that hSMCT1, which is a candidate of the PA uptake transporter at the renal apical side, stimulates urate transport via hURAT1 by forming an outward concentration gradient of PA in an in vitro study, and the mRNA distribution of URAT1 overlaps that of SMCT1 in mouse kidney. The IC50 values of PRB for hURAT1 and hSMCT1 were comparable (50 and 139 μM, respectively), while BZB did not interact with hSMCT1 by 100μM). Therefore, it is suggested that PRB competes for an antiuricosuric effect of pyrazinamide, thereby exhibiting a uricosuric effect in patients treated with pyrazinamide. 1) Z Yu. et al, Drug Metab Dispos., 35:981, 2007

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ACTIVATION OF MORPHINE UDP-GLUCURONOSYLTRANSFERASES BY FATTY ACYL-COA IN HUMAN AND RAT
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Morphine is still an important medicine of the standard choice for the relief of moderate to severe pain. Morphine is conjugated by UGT to 3- and 6-glucuronides (M-3-G and M-6-G, respectively). M-3-G is non-analgesic while M-6-G is potent analgesic than parent morphine. We have reported previously that fatty acyl-CoAs are the endogenous activators of 4-methylumbelliferone UGT in rat liver microsomes. To clarify whether the same occurs for different substrates and in other species, the effects of fatty acyl-CoAs on morphine glucuronidation were examined using human as well as rat liver microsomes. Oleoyl (C18:1)- and palmitoyl (C16:0)-CoAs inhibited M-3-G formation catalyzed by Brij 58-treated rat liver microsomes. However, both acyl-CoAs up to 15 μM enhanced the UGT activity catalyzed by untreated microsomes, whereas the acyl-CoA at concentration 50 μM or higher were inhibitory. Other medium- to long-chain acyl-CoAs also exhibited a similar activating profile. A kinetic analysis of the acyl-CoA-produced activation showed that, while the Km for UDP-glucuronic acid was reduced by acyl-CoA treatment, the Vmax was increased, resulting in the 8-fold increase of the intrinsic clearance (Vmax/Km). Since fatty acids can be released from acyl-CoAs, the effect of fatty acids on the UGT activity was also investigated. Unsaturated fatty acids at 15 μM showed only minor activating effects. Similarly, saturated fatty acids did not show any effect. Oleoyl-CoA inhibited morphine glucuronidation activity catalyzed by UGT2B7 supersomes in spite of the absence of detergent. However, similarly to rat liver microsomes, 15 μM oleoyl-CoA significantly activated M-3-G and M-6-G formation catalyzed by some of the human liver microsomes not treated with detergent. The data obtained suggest that 1) fatty acyl-CoAs activate UGT-catalyzed morphine glucuronidation in intact rat and human liver microsomes by a mechanism different from that by fatty acid; and 2) a change in the endogenous acyl-CoA level greatly affects not only the elimination of morphine but also the formation of active metabolite, M-6-G.